OAR Box 1851

Prepped by Keeia Richards

Document Number:

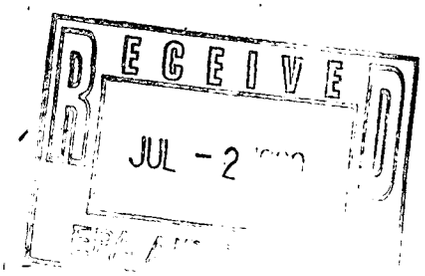
18) IV-F-2

Docket Number:

A-90-16

A-90-16
IV-F-2

June 19, 1990



AIR DOCKET (LE-131)
US Environmental Protection Agency
Room M-1500
401 M Street SW
Washington, D.C. 20460

COMMENTS OF THE ENVIRONMENTAL DEFENSE FUND ON THE WAIVER APPLICATION BY ETHYL CORPORATION FOR METHYCYCLOPENTADIENYL MANGANESE TRICARBONYL (MMT) AS A GASOLINE ADDITIVE

The Environmental Defense Fund submits these comments on the application by the Ethyl Corporation to add MMT, an organomanganese compound, to gasoline as an octane enhancer. EDF is a national, nonprofit, environmental research and advocacy organization with over 100,000 members throughout the United States. These comments are prepared by Ellen K. Silbergeld, Ph.D., Senior Scientist and Director of the Toxic Chemicals Program. EDF intends to submit an expanded version of these comments before the close of the public comment period; this document is for purposes of the public hearing.

Over the past decade, I have served on several EPA committees charged with assessing environmental fate and transport, exposure, and health impacts of another organometal gasoline additive also manufactured by Ethyl tetraethyl lead. In addition, I have provided comments on request to the governments of Canada, Bermuda, Thailand, and Mexico on the topic of lead additives to gasoline. Since receiving my Ph.D. from Johns Hopkins in 1972, I have actively conducted basic and clinical research on the effects of low level chronic exposure to both lead and manganese. While I was at NIH, I provided expert opinion via the Director of NINCDS to the government of Bolivia on the potential effects of manganese in drinking water. More recently, I was a peer reviewer of EPA's most recent health assessment of manganese. I also reviewed the recent Health Effects Institute paper on the health effects of manganese as an additive to gasoline.

Earlier this month, I met with two representatives of Ethyl, Dr. Gary Ter Haar and Dr. Donald Lynam, at their request, to hear their position in support of Ethyl's application to use MMT in unleaded gasoline. I am aware of the arguments and data upon which Ethyl's application is based.

<u>EDF strongly opposes granting this waiver application.</u> The Clean Air Act provides that EPA "may" grant a waiver allowing the use of manganese as a fuel additive upon determining that the additive will not impair emissions control devices such as the catalytic converter. Regardless of the effects of MMT on emissions control, there is no dispute that manganese is neurotoxic to humans. On this basis, EPA should deny this waiver, particularly since Ethyl has failed yet again to provide relevant or convincing evidence that use of MMT will not affect

human health. EDF believes that it would be an abrogation of EPA's clear responsibility under the Clean Air Act to protect human health, to do otherwise.

It is rare that an opportunity arises to apply the clear lessons of the past 50 years' experience with a very similar application. To disregard these lessons by approving the widespread and inherently dispersive use of another neurotoxic metal would be to invite repetition of the public health catastrophe associated with the use of lead as a gasoline additive from 1925 to the present. The 1988 ATSDR report to Congress on childhood lead poisoning documents that lead toxicity is an epidemic in the United States. Even after considerable reductions have been imposed on the use of lead in gasoline -- after prolonged debate and litigation, it should be noted -- we are only now confronting the extraordinarily difficult challenge of cleaning up the residues of lead fallout from city playgrounds, school yards, and backyards around America. Dr. Katherine Farrell and Dr. Boon Lim, of the Maryland Department of Environment, are currently conducting research, sponsored by EPA, on the significance of soil lead as a source of exposure for urban children; a recent report from the California Department of Health Services already demonstrates the quantitative relationship between soil lead and childrens' blood lead levels.

This is an experience we cannot afford to repeat. The parallels between Ethyl's proposal in 1990, to use manganese, and its proposal in 1925, to use lead, are chilling. In both cases, the exclusive basis for this application is its purported effect on emissions of hydrocarbons and NOx from cars. No data were or are submitted on the potential cumulative health effects of massive inputs of a toxic metal into the environment, its deposition into surface dusts and soils, and its longerm fate and exposure pathways to humans. In 1925, Ethyl argued that the amounts of lead to be added to gasoline were of negligible importance, and that lead was only toxic at the high doses encountered in certain industrial settings. In 1990, Ethyl argues that the releases of manganese to the environment will be insignificant and that manganese is only toxic at high doses in industrial settings. In both cases, Ethyl has suggested that acceptance of its additive is of critical importance to the nation (see generally Rosner and Markowitz (1983) [attached] for the historical perspective on Ethyl's campaign to secure acceptance of tetraethyllead).

In 1925, over the prophetic objections of Dr. A. Hamilton and Y. Henderson, the U.S. Public Health Service acquiesced in approving Ethyl's application despite the absence of any data the impact of lead additives on environmental concentrations of lead or the health effects of low level, chronic lead exposure, particularly in children. The PHS urged that these and other issues be considered in a reevaluation to be conducted at some later point; this reevaluation did not commence until 1977. By then, millions of tons of lead had been spread throughout America.

In 1990, amazingly, Ethyl finds it unnecessary to do anything more than it did in 1925. Wholly inadequate data are presented to indicate that adding manganese to gasoline does not change concentrations of manganese in ambient air over the short term in some selected Canadian cities. Ethyl does not cite a recent study from California indicating that increases in airborne manganese in air samples are related to additions of manganese to gasoline already permitted by EPA (see Davis, et al, 1988; references attached). No in-depth discussion of the health effects of manganese is presented, nor -- more importantly -- is there a discussion of the critical datagaps on manganese toxicity that must be filled before any decision can be approved that would result in tons of manganese released into the environment (see attached bibliography).

EPA must assert its leadership role in 1990 to defend the preventive imperative of its mandate to protect human health and the environment. What is at stake is not the health of emission control devices in automobiles but the health of humans. This waiver cannot be approved until the applicant provides substantive information on the cumulative impacts of manganese additives on environmental quality (not solely ambient air concentrations) and convincing evidence that such impacts will not adversely affect the health of any segment of the human population over the longterm.

In making this case, Ethyl must demonstrate that the likely experience with manganese will not resemble that with lead. This demonstration will be difficult. Both lead and manganese are elements and as such will not degrade or quickly disappear from stable environmental compartments, such as soils, dusts, and sediments. Patterns of use will result in relative enrichment in urban, densely populated areas with high levels of vehicular traffic and residential patterns such that persons are in close contact with the areas most heavily impacted by fallout from vehicle emissions. While the proposed per gallon usage of manganese is less than the usage of lead in gasoline at its peak prior to regulation in 1978, the vastly increased amount of gasoline consumed and number of vehicle miles driven in the U.S. in 1990 as compared to 1925 will ensure that the rate of contamination of our environment from this source will be comparable.

Both lead and manganese are neurotoxic metals. While the data on manganese is relatively sparse (compared to lead -- but we have not yet conducted a massive human experiment with manganese), the hazard identification of manganese as a neurotoxin and lung toxin is clear (see generally EPA's HAD on manganese and attached bibliography). Manganese, like lead, is a cumulative toxin in that both its absorption and retention as well as its toxicity increase with time. At present, there are insufficient data on the low level, chronic sequelae of manganese exposure -- similar to the case for lead in 1925 as noted above. There are no data on the effects of manganese on the ageing

brain, although it has been suggested that the nature of manganese-induced pathophysiology -- damage to the nigrostriatal system -- is such that interaction with normal cell loss during senescence would be expected. The potential for selective susceptibility to manganese in the aged must be of great concern as the U.S. population ages. Studies on the population of Groote Eylandt disease by Cawte (which I was one of the first persons to review over ten years ago) suggest that there may also be fetal and early developmental effects of manganese. The possibility that iron deficiency may potentiate manganese toxicity is of considerable concern, given the prevalence of iron deficiency in the U.S. (see NHANES II data).

The mechanisms by which manganese damages neural tissue (particularly catecholaminergic pathways) are unknown, so that we cannot propose an overall dose response relationship or rational basis for risk assessment. There are inadequate studies on the immunotoxic effects of MMT or manganese. The toxicokinetics of low dose manganese exposure are not known; the observations of apparent decreases in brain manganese concentrations with prolonged exposure are at relatively high exposures and may reflect a pathological effect (e.g., loss of normal Mn binding sites, such as enzymes or other proteins) rather than a protective effect. These rather odd toxicokinetics have not been replicated in primates. Moreover, as the study by Yamada et al indicates, the expression of severe akinetic and neuropsychiatric symptoms were not associated with increased concentrations of manganese in brain, further indicating that the mechanisms as well as the toxicokinetics of manganese are not well understood. No defined biological markers for manganese exposure in humans have been validated, so that interpretation of epidemiological studies is limited.

In summary both what we know and do not know at present about the likely toxic effects of adding manganese in large total amounts to the environment must persuade EPA to reject this application. We know that manganese at high dose is a demonstrated human neurotoxin, with persistent and irreversible pathological effects on brain structure and resulting severe impairments in movement and mental state. We do not know what the longterm, chronic, low dose consequences of human exposure to manganese are. We do not know a "safe" level of manganese exposure, particularly for those subgroups that may be at increased risk for neurotoxicity (the young and the aged). We do not know if manganese is carcinogenic, although there is evidence that it can break DNA.

With respect to exposure assessment in contrast, we kno great deal, based upon our tragic experience with lead, ab likely cumulative impacts of such a use upon human exposu manganese. We know that the gradual contamination of th environment by this additive will not be readily rever

that manganese will accumulate in specific parts of the environment, many of which are subject to intensive human interaction (urban dusts and soils). We know that manganese in air and in surface dusts and soils will be present directly to humans as a source of exposure.

Ethyl has chosen to focus in its application on the purported efficacy of manganese additives to reduce certain pollutant emissions from vehicles. In a well mounted publicity campaign over the past week, Ethyl has sought to harness concerns over the impacts of these air pollutants on global and local air quality as justification. Ethyl has selectively cited bits of data in support of its contention that use of MMT will not increase manganese concentrations in air in cities. Ethyl has provided no data on impacts of manganese additives on manganese concentrations in more stable postdeposition compartments, such as dusts and soils. Ethyl has provided no in depth review of the data and datagaps on manganese toxicity.

In 1925, Ethyl introduced its new product tetraethyllead as "a gift of God." It has taken us over 50 years to realize how diabolical this "gift" has proven to be. The reduction of lead in gasoline represents one of the most significant public health achievements of the EPA. I am proud to have participated in that victory. Now in 1990 Ethyl comes bearing yet another gift. To this offering, EPA must just say "No." The purported "benefits" of reducing climatic impacts cannot be achieved upon the rack of an epidemic of manganism. EDF urges rejection of this application and immediate suspension of all permitted use of manganese as a gasoline additive in the U.S.

A-90-16
IV-F-2

Output generated from Compact Cambridge: POLTOX 1987 - March 1990
Search Strategy:
((MANGANESE[ALL] OR MN[ALL]) AND (AIR[ALL] OR SOIL[ALL] OR SOILS[ALL] OR LAND[ALL] OR GROUND[ALL])) AND ((PETROL[ALL] OR PETROLEUM[ALL] OR (GAS[ALL] OR GASOLINE[ALL]))
DOCUMENT 7 of 17:

AU: AUTHOR
Davis DW; Hsiao K; Ingels R; Shikiya J
TI: TITLE
Origins of manganese in air particulates in California.
SO: SOURCE
J. AIR POLLUT. CONTROL ASSOC.; vol. 38, no. 9, pp. 1152-1157; 1988
PY: PUBLICATION YEAR
1988.
LA: LANGUAGE
English
AB: ABSTRACT
The proportions of manganese to other metals in samples of air-borne fine particles taken at some sites in California have increased greatly since the beginning of 1985. Here, data are presented which indicate that the addition of manganese to leaded gasoline is largely responsible for this increase. Concentrations of manganese, silicon, titanium, iron, lead and other elements in airborne particles were measured using energy-dispersive X-ray fluorescence analysis. Coefficients of correlation among levels of manganese, iron and lead measured at twenty sites in California were calculated. Levels of manganese and iron are generally highly correlated because of the presence of large amounts of these elements in the earth's crust. Levels of airborne manganese and lead at sites in Southern California are often highly correlated, suggesting a vehicular source of manganese.
ABSTRACT.

SF: NIOSH
TI: The Present Status Of Biological Effects Of Toxic Metals In The Environment: Lead, Cadmium, And **Manganese**
AU: Shukla-GS; Singhal-RL
SO: Canadian Journal of Physiology and Pharmacology, Vol. 62, No. 6, pages 1015-1031, 187 references, 1984
AB: Lead (7439921), cadmium (7440-43), and **manganese** (7439965) toxicities are reviewed. The sources of these metals and their presence in **air**, water, soil, and food is addressed. Experimental and epidemiological studies of exposure are reviewed. Emphasis has been placed on nervous system effects from

exposure to low concentrations. These metals appear to produce behavioral changes by altering the metabolism of brain neurotransmitters. Clinical and animal data show that lead and **manganese** are most toxic to the nervous system, while cadmium exerts adverse effects on the kidney and the male reproductive system. It is hypothesized that the metals exert their toxic effects by damaging biologic defenses that exist in the body to serve as protective mechanism against exogenous toxins. The importance of studying combined health effects of toxins is emphasized; humans are exposed simultaneously or successively to different physical, chemical, biological, and psychological factors, and other factors such as drug therapy, cigarette smoking, alcohol ingestion, and coexistent disease may influence individual susceptibility to these metals. Thus, at very low concentrations of a single metal, there may be severe impairment of absorption, distribution, receptor sites, or elimination of the toxic substance. Evidence shows that metals are capable of interacting with biologically important cellular systems at doses below those required to produce signs of overt toxicity. The authors conclude that it is essential to develop an appropriate model of metal toxicity that can serve as a predictive tool of toxic manifestations when encountered in combination with other metallotoxins.
AN: 00147720

SilverPlatter 1.6 TOXLINE (R) 1981 - 1987

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SF: NIISH
TI: Uptake, Distribution, And Behavioral Effects Of Inhalation Exposure To **Manganese** (MnO2) In The Adult Mouse
AU: Morganti-JE; Lown-BA; Steineman-CH; D'Agostino-RB; Massaro-EJ
SO: NeuroToxicology, Vol. 6, No. 1, pages 1-16, 32 references, 1985
AB: The uptake, distribution, and behavioral effects of inhalation exposure to **manganese** (7439965) were studied in mice. Male ICR-Swiss-mice were exposed to **manganese-dioxide** (1313139) dust or filtered **air** 7 hours per day, 5 days per week for 16 to 32 weeks. Exposure concentrations were 49.1 milligrams per cubic meter (mg/m3) for the first 12 weeks and 85.3mg/m3 thereafter. Selected animals were observed for behavioral performance (ambulations and rearings in the open field, hole in the board exploration) and passive avoidance learning at weeks 16, 20, 24, 28, and 32. Body weights were measured. They were then killed and organs and tissues were taken and assayed for **manganese**. Tissue samples were examined for histopathological changes. **Manganese** exposed mice executed a significantly larger number of rearings in the open field and tended to show longer latencies to enter the open field. The exposed mice had higher body weights than control animals. **Manganese** exposed animals had significantly higher blood, liver, kidney, lung, cerebrum, cerebellum plus brain stem, and testes **manganese** concentrations than controls. With the exception of the liver, the **manganese** concentrations decreased with increasing exposure time after 20 weeks. Liver **manganese** concentrations increased with increasing exposure time. **Manganese-dioxide** exposure caused no detectable histopathological changes. The authors conclude that inhalation exposure to **manganese** has significant effects on mouse behavior, particularly those behaviors having an activity component, and causes a transient increase in tissue **manganese** concentrations. The decrease in tissue **manganese** concentrations observed in all organs except the liver would appear to have a protective function.
AN: 00149096

SilverPlatter 1.6 TOXLINE (R) 1981 - 1987

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SF: NIOSH
TI: Preclinical Toxic Effects Of **Manganese** In Workers From A **Mn** Salts And Oxides Producing Plant
AU: Roels-H; Sarhan-MJ; Hanotiau-I; de-Fays-M; Genet-P; Bernard-A; Buchet-JP; Lauwerys-R
SO: Science of the Total Environment, Vol. 42, No. 1-2, pages 201-206, 18 references, 1985
AB: An epidemiological study of workers from a **manganese**-(7439954) salts and oxides producing facility (SIC-2819) was conducted. The cohort consisted of 245 male subjects divided into 104 comparisons and 141 **manganese** exposed workers. **Manganese**-exposed workers were occupied at 11 workplaces. Total airborne **manganese** dust was monitored with personal samplers. Each subject was examined according to the following protocol: self-administered questionnaire; neurological examination; records of maximal expiratory flow volume curves, forced vital capacity (FVC), forced expiratory volume (FEV), peak expiratory flow rate (PEFR), and maximal expiratory flow rate (MEFR); psychomotor tests; and biological analyses. No relationship was found between **manganese** in blood and **manganese** in urine. There was no correlation between the concentrations of **manganese** in blood of each of the comparisons or exposed subjects and the current concentrations of **manganese** in **air** at each workplace. There was no correlation between duration of exposure and **manganese** in blood or **manganese** in urine. Analysis of the questionnaire revealed higher prevalences of cough, sputum, dyspnea, and acute bronchitis in the **manganese** exposed workers. Lung functions were mild and showed a slight decrease in MEFR at 50 and 75 percent of FVC in **manganese** exposed nonsmokers and a statistically significant difference in FVC, FEV, and PEFR between comparison smokers and **manganese** exposed smokers. Significant differences were found for fatigue, tinnitus, trembling of fingers, and increased irritability in **manganese** exposed workers. **Manganese** exposed workers performed less well during the psychomotor tests, and abnormal score values were higher for eye to hand coordination, hand steadiness, short term memory, and simple reaction time. The hematological data of **manganese** exposed workers did not differ from that for the comparison group. The authors suggest that preclinical perturbations may occur in subjects exposed to airborne **manganese** concentrations that are lower than concentrations actually tolerated
AN: 00147456

Output generated from Compact Cambridge: POLTOX 1987 - March 1990
Search Strategy:
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DOCUMENT 47 of 85:

AU: AUTHOR
Donaldson J
TI: TITLE
The Physiopathologic Significance of Manganese in Brain: Its Relation to Schizophrenia and Neurodegenerative Disorders
SO: SOURCE
NeuroToxicology, Vol. 8, No. 3, pages 451-462, 48 references, 1987
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
The physiopathology of elevated brain manganese (7439965) (Mn) was reviewed with the purpose of elucidating mechanisms of Mn neurotoxicity. Animal models of Mn pathology, case studies of Locura-manganica or manganese madness, the Groote Eylandt syndrome, chronic manganism, and manganese psychosis were discussed. Common observations included melanin loss, degeneration of the striatum or its components, and alterations in central dopaminergic receptors implying dopamine oxidation as a mechanism of Mn pathology. Hypotheses for Mn pathology reviewed included Mn induced enhancement of dopamine autooxidation, Mn catalyzed production of toxic catecholamines, Mn-self-oxidation and dismutation with resulting oxidative destruction of dopamine, and catecholamine oxidation by trivalent Mn. The role of zinc in protecting against Mn induced dopamine oxidation was attributed to the affinity of zinc ions for hydroxyl moieties and to the involvement of zinc in maintaining redox balance and membrane stability. The author suggests that tissue susceptibility to Mn toxic effects in the brain are related to the redox bioenergetic status of the various tissues and that other tissues with elevated levels of oxidative enzymes (oxidases, peroxides) such as testes, pancreatic-B cells, and macrophages would show similar sensitivity to Mn insult. ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1967 - March 1990
Search Strategy:
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DOCUMENT 80 of 85:

AU: AUTHOR
Archibald FS; Tyree C
TI: TITLE
Manganese poisoning and the attack of trivalent manganese upon catecholamines.
SO: SOURCE
Arch Biochem Biophys; VOL 256, ISS 2, 1987, P638-50
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
Human manganese poisoning or manganism results in damage to the substantia nigra of the brain stem, a drop in the level of the inhibitory neurotransmitter dopamine, and symptoms resembling those of Parkinson's disease. Manganic (Mn3+) manganese ions were shown to be readily produced by O-2 in vitro and spontaneously under conditions obtainable in the human brain. Mn3+ as its pyrophosphate complex was shown to rapidly and efficiently carry out four-electron oxidations of dopamine, its precursor dopa (3,4-dihydroxyphenylalanine), and its biosynthetic products epinephrine and norepinephrine. Mn3+-pyrophosphate was shown to specifically attack dihydroxybenzene derivatives, but only those with adjacent hydroxyl groups. Further, the addition of Mn2+-pyrophosphate to a system containing a flux of O2- and dopamine greatly accelerated the oxidation of dopamine. The oxidation of dopamine by Mn3+ neither produced nor required O2, and Mn3+ was far more efficient than Mn2+, Mn4+ (MnO2), O2-, or H2O2 in oxidizing the catecholamines. A higher oxidation state, Mn(OH)3, formed spontaneously in an aqueous Mn(OH)2 precipitate and slowly darkened, presumably being oxidized to MnO2. Like reagent MnO2, it weakly catalyzed dopamine oxidation. However, both MnO2 preparations showed dramatically increased abilities to oxidize dopamine in the presence of pyrophosphate due to enhancement of the spontaneous formation of the Mn3+ complex. These results strongly suggest that the pathology of manganese neurotoxicity is dependent on the ease with which simple Mn3+ complexes are formed under physiological conditions and the efficiency with which they destroy catecholamines. ABSTRACT.

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DOCUMENT 58 of 85:

AU: AUTHOR
Kilburn CJ
TI: TITLE
Manganese, malformations and motor disorders: Findings in a manganese-exposed population.
SO: SOURCE
NEUROTOXICOLOGY.; vol. 8, no. 3, pp. 421-430; 1987
PY: PUBLICATION YEAR
1987.
LA: LANGUAGE
English
AB: ABSTRACT
This study attempts to further delineate aspects of the Groote Eylandt syndrome, and by examining birth records and children, to explore the possible effects of manganese during fetal and neonatal development. This focus on the childhood population is in accord with both the clinical expertise of the investigator and with experimental evidence which suggests that manganese may be a particular hazard during fetal and neonatal development. ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990
Search Strategy:
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DOCUMENT 60 of 85:

AU: AUTHOR
Eriksson H; Magliste K; Plantin LO; Fonnum F; Hedstrom KG; Theodorsson-Norheim E; Kristensson K; Stalberg E; Heilbronn E
TI: TITLE
Effects of manganese oxide on monkeys as revealed by a combined neurochemical, histological and neurophysiological evaluation.
SO: SOURCE
Arch Toxicol; VOL 61, ISS 1, 1987, P46-52
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
Four monkeys were exposed to a total of 8 g each of manganese as oxide by repetitive subcutaneous injections during 5 months, after which they were left for 1 week to 6 months before they were sacrificed. All animals developed hyperactive behaviour after about 2 months. About 5 months after the start of the exposure the animals became hypoactive with an unsteady gait, and subsequently an action tremor appeared in some of the animals. The animals lost power in both upper and lower limbs and the movements of the hands and feet were very clumsy. The serum content of manganese rose 10-40 times during the exposure time and the content in brain was generally increased more than 10 times, with the highest content found in globus pallidus and putamen. The observed neurochemical effects were also largest in globus pallidus and putamen. In these regions there was a considerable depletion of dopamine and 3,4-dihydroxyphenylacetic acid, while the homovanillic acid content remained almost unchanged. A severe neuronal cell loss was observed in globus pallidus but not in other regions. This is in accordance with results from the most recent neuropathological study of a human suffering from chronic manganese poisoning [Yamada et al. (1986) Acta Neuropathol 70: 273-278] where globus pallidus was devoid of neuronal cells while the content of pigmented cells in substantia nigra was normal. Our data suggest a reduction in number of dopaminergic nerve terminals, as the activity of the dopamine synthesizing enzyme DOPA-decarboxylase was also lowered.(ABSTRACT TRUNCATED AT 250 WORDS) ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990
Search Strategy:
MANGANESE[ALL] OR MN[ALL] AND (NEUROTOX*[ALL] OR NEUROTRANSMIT*[ALL] OR NEUROL*G*[ALL] OR NEUROP-TH*[ALL] OR (NERVE[ALL] OR NERVES[ALL] OR NERVOUS[ALL]) AND MANGANESE[ALL]
DOCUMENT 59 of 85:

AU: AUTHOR
Roels H; Lauwerys R; Buchet J-P; Genet P; Sarhan MJ; Hanotiau I; de Fays M; Bernard A; Stanescu D
TI: TITLE
Epidemiological Survey Among Workers Exposed to Manganese: Effects on Lung, Central Nervous System, and Some Biological Indices
SO: SOURCE
American Journal of Industrial Medicine, Vol. 11, No. 3, pages 307-327, 56 references, 1987
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
An epidemiological survey was conducted to evaluate the effects of exposure to manganese (7439965) on the lung, central nervous system, and selected physiological parameters of industrial workers. A group of 141 male workers exposed to manganese formed the experimental group and were compared to 104 comparison subjects. Relative to the comparison group, the exposed group exhibited an increased tendency towards developing coughs in the winter, dyspnea during exercise, and incidences of acute bronchitis. The lung function parameters such as forced vital capacity, peak expiratory flow rate, and others were only mildly changed in exposed workers who were also either previous or current smokers. Smoking and manganese exposure showed no synergy, nor were the changes in smokers related to manganese levels in blood or urine. There was a small increase in the prevalence of fatigue, irritability, tinnitus and trembling of fingers in the exposed workers. Exposure to manganese had significant adverse effects on audio verbal short term memory capacity, eye hand coordination, reaction time and steadiness of the hand. The manganese group also had altered serum levels of ferritin, calcium, copper, and ceruloplasmin. Exposed workers had an increased number of circulating neutrophils. Changes in these biological and neurological parameters were not related to exposure levels in a dose dependent fashion. Hand tremors, eye hand coordination and blood calcium levels were related to manganese levels in blood. The authors conclude that a time weighted average exposure to manganese dust at 1mg/m3 for less than 20 years may result in preclinical signs of intoxication. ABSTRACT.

SF: TOXEIB
TI: Chronic **manganese** poisoning: a **neuropathological** study with determination of **manganese** distribution in the brain.
AU: Yamada-M; Ohno-S; Okayasu-I; Okeda-R; Hatakeyama-S; Watanabe-H; Ushio-K; Tsukagoshi-H
SO: **Acta-Neuropathol-Berl**; VOL 70, ISS 3-4, 1986, P273-8
AB: An autopsy case of a 52-year-old man suffering from chronic **manganese** poisoning (CMP) is reported with determination of the **manganese** distribution in the brain. The patient had been working in a **manganese** ore crushing plant since 1965. In 1967 he began to complain of difficulties in walking and diminished libido. Later, he developed various neuropsychiatric symptoms including euphoria, emotional incontinence, masked face, monotonous speech, "cock-walk", increased muscle tone, weakness of upper and lower extremities, tremor of the eye lids, and exaggeration of knee jerks. The major **neuropathological** change was degeneration of the basal ganglia, in which the pallidum was severely affected. The pallidum disclosed a loss and degeneration of **nerve** cells, which was especially marked in the medial segment, a prominent decrease of myelinated fibers, and moderate astrocytic proliferation. The substantia nigra was intact. Distribution of **manganese** in the brain of the present case of CMP was determined using flameless atomic absorption spectrometry and compared with control cases and also a case of Parkinson's disease (PD). There was no significant difference between the control cases and the case of PD in average concentration of **manganese** and its distribution in the brain. The present case of CMP showed no elevation in average concentration of **manganese** in the brain. However, there were some changes in its distribution. Thus, the continuance of **neurological** disorders in CMP is not linked to an elevated **manganese** concentration itself in the brain. CMP appears to be different from PD in **neuropathology** and **manganese** behavior in brain.
AN: 87022052

SilverPlatter 1.6 TOXLINE (R) 1981 - 1987

28 of 118

SF: ETIC
TI: BRAIN **MANGANESE**, CATECHOLAMINE TURNOVER, AND THE DEVELOPMENT OF STARTLE IN RATS PRENATALLY EXPOSED TO **MANGANESE**
AU: MONTUR-PJ; FECHTER-LD
SO: TERATOLOGY; 32:1-11,1985
AB: ETIC/ORNL
AN: 85037574

31 of 118

SF: TOXBIB
TI: Effect of low protein diet on **manganese neurotoxicity**: III. Brain **neurotransmitter** levels.
AU: Ali-MM; Murthy-RC; Mandal-SK; Chandra-SV
SO: Neurobehav-Toxicol-Teratol; VOL 7, ISS 5, 1985, P427-31
AB: The effect of concurrent low protein (10% casein) diet and **manganese** (**Mn**) exposure (3 mg/ml drinking water) on brain levels of dopamine (DA), norepinephrine (NE) and 5-hydroxytryptamine (5-HT) were investigated in Fo-growing (90 days exposure), Fo-diet rehabilitated (low----normal protein diet-28 days) and F1-weaned rats. **Mn** exposure in either diet group resulted in a significant increase in the DA and NE levels but a decrease in the 5-HT level. These effects were more pronounced in the rats fed the low protein diet, especially in the F1-offsprings. Diet rehabilitation reduced the effects of **Mn** exposure.
AN: 86092419

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SF: TOXBIB
TI: .Biological aspects of occupational exposure to cadmium and several other metals.
AU: Lauwerys-R; Buchet-JP; Roels-H; Bernard-A; Gennart-JP
SO: Rev-Epidemiol-Sante-Publique; VOL 34, ISS 4-5, 1986, P280-5
AB: We have performed several cross-sectional epidemiological surveys among workers exposed to cadmium, mercury vapour or **manganese** in order to assess : their early biological or functional effects; the biological tests allowing an assessment of the amount of metal absorbed or stored in the body; the acceptable exposure levels. Studies have also been carried out among persons exposed to inorganic arsenic in order to define its inactivation mechanism and to develop a biological test of exposure. The kidney is the main critical organ following long-term exposure to cadmium. To prevent the occurrence of renal changes in the majority of male workers exposed to cadmium, its concentration in renal cortex should not exceed 215 micrograms/g (wet weight), and that in urine : 10 micrograms/g creatinine. A blood cadmium level of 1 microgram/100 ml has been suggested as maximum tolerable level for long-term exposure. Prolonged exposure to mercury vapour may lead to renal and **neurological** disturbances. The preclinical signs of nephrotoxicity are correlated with the amount of mercury absorbed which may be assessed by monitoring the mercury level in urine. The **neurotoxic** effects (particularly tremor) are mainly related to the integrated exposure (duration and intensity). A maximal permissible level of 50 micrograms Hg/g urinary creatinine is proposed to prevent the occurrence of these toxic effects. An exposure to **manganese** dust for 7 years on the average at a level below the maximum allowable airborne concentration (5 mg/m3) recommended by the ACGIH in the USA may still lead to a slight reduction in psychomotor and spirometric performances and interfere with calcium metabolism.(ABSTRACT TRUNCATED AT 250 WORDS)
AN: 87148228

DF: TOXBIB
TI: Effects of **manganese** chloride on the rat developing **nervous** system.
AU: Kristensson-K; Eriksson-H; Lundh-B; Plantin-LO; Wachtmeister-L; el-Azazi-M; Morath-C; Heilbronn-E
SO: Acta-Pharmacol-Toxicol-Copenh; VOL 59, ISS 5, 1986, P345-8
AB: Sprague-Dawley rats were exposed to sublethal doses of **manganese** chloride during their postnatal development period up to 44 days of age. They showed transient clinical signs of disease and a decreased homovanillic acid (HVA) content in the striatum and hypothalamus between 15 and 22 days of age. The **manganese** content in the brain was increased 20-40 times during this period as determined with neutron activation analyses. In spite of this no structural damage or signs of maturation disturbances in the **nervous** system were found. Interruption of **manganese** exposure reversed the changes in HVA content.
AN: 87123569

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SF: NIOSH
TI: **Manganese** Absorption and Metabolism in Man
AU: Sandstrom-B; Davidsson-L; Cederblad-A; Eriksson-R; Lonnerdal-B
SO: Acta Pharmacologica et Toxicologica, Vol. 59, Supplement VII, pages 60-62, 4 references, 1986
AB: The absorption and metabolism of **manganese** (7439965) was studied in healthy adults using a radioactive tracer. Fourteen health volunteers, ages 20 to 38 years, received either a test meal or a mineral solution containing labeled **manganese**. Whole body retention measurements with scintillators were made daily for the first 2 weeks and then weekly for up to 6 months. Two subjects were subsequently given intravenous injections of labeled **manganese** 6 months after oral administration and whole body retention was monitored in a similar manner. The biological half life of the radioisotope after oral administration was 13 +/8 days for the first 20 days, and 34 +/8 days for days 20 through 50. In the two subjects that received **manganese** both orally and intravenously, the biological half lives for the first 20 days after oral administration were 8 and 15 days, and 23 and 65 days, respectively, after intravenous administration. **Manganese** absorption was measured after oral intake of 450 milliliters of cow's milk baby formula containing 50 micrograms per liter **manganese**, or a multielemental preparation containing 2.5 milligrams **manganese**. The absorption of **manganese** from the infant formula was 8.4 +/4.7 percent, with the exception of one subject with iron deficiency anemia, in whom 45.5 percent of the **manganese** was absorbed. Absorption from the multielemental preparation was 8.9 +/3.2 percent. The authors conclude that the metabolism of **manganese** is dependent on the route of administration and va
ries greatly between individuals. The authors further conclude that iron deficiency anemia substantially increases **manganese** absorption and may increase the risk of **manganese** toxicity.
AN: 00166706

13 of 118

SF: NIOSH
TI: Behavioral Effects of Chronic **Manganese** Administration in Rats: Locomotor Activity Studies
AU: Nachtman-JP; Tubben-RE; Commissaris-RL
SO: Neurobehavioral Toxicology and Teratology, Vol. 8, No. 5, pages 711-715, 19 references, 1986
AB: The effects of chronic administration of **manganese** (7439965) (**Mn**) on behavior in rats were tested using a measure of locomotor activity. Male Sprague-Dawley-rats were provided with drinking water containing 0 or 1mg/ml of **manganese-chloride** (7773015) (MnCl2). **Mn** did not affect body weights. After 14, 29, 41, and 65 weeks, the locomotor stimulant effects of administration of d-amphetamine (300629) were determined. Locomotor activity was increased in **Mn** treated rats at weeks five, six, and seven, but subsequently returning to control levels. Activity levels were higher in **Mn** treated animals. **Mn** treatment had no effect on habituation. By week 13 there was no **Mn** effect. d-Amphetamine significantly increased activity, and the observed interaction effect indicated greater stimulating effect of d-amphetamine in **Mn** treated animals. At weeks 41 and 65, there was no difference in the responsiveness of the two groups to the stimulant effects of d-amphetamine. The authors conclude that oral exposure of rats to a low dose of **Mn** resulted in a transient increase in both basal and d-amphetamine stimulated activity. These effects may represent an animal model for the "**manganese** madness" phase of **Mn** toxicity in humans.
AN: 00166953

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SF: TOXBIB
TI: Effect of low protein diet on **manganese** neurotoxicity: I. Developmental and biochemical changes.
AU: Ali-MM; Murthy-RC; Saxena-DK; Srivastava-RS; Chandra-SV
SO: Neurobehav-Toxicol-Teratol; VOL 5, ISS 3, 1983, P377-83
AB: The first in a series of studies on the effect of concurrent low protein diet (10% casein) and **manganese** exposure (Mn2+, 3 mg/ml drinking water) in rats is reported here. The effect on growing (Fo-90 days) rehabilitated (Fo low leads to normal protein diet-28 days) and the F1 generation pups (weaned) were studied. Mn2+ exposure had no significant effect on growth pattern, brain weight or brain and plasma protein contents in either dietary groups. The diet regimen had no significant effect on the accumulation of Mn2+ in brain in any of the groups studied but the levels were higher in the F1 pups than in the parent (Fo) generation. In the F1 pups Mn2+ exposure had no effect on eye opening in either dietary group, delayed the development of startle reflex in low protein fed group only but the **air** righting reflex development was delayed in both the dietary groups, the effect being more marked in the low protein fed group. These changes reflect the early neurotoxic effect of Mn2+.
MESH: Animal-; Blood-Proteins-metabolism; Brain-metabolism; Female-; Male-; Nerve-Tissue-Proteins-metabolism; Organ-Weight-drug-effects; Protein-Calorie-Malnutrition-metabolism; Rats-
MESH: *Brain-drug-effects; *Dietary-Proteins-pharmacology; *Growth-drug-effects; ***Manganese-toxicity**; *Protein-Calorie-Malnutrition-complications
AN: 83271721

65 of 82

SF: NIOSH
TI: The Effect Of **Manganese** Inhalation On Basal Ganglia Dopamine Concentrations In Rhesus Monkey
AU: Eird-ED; Anton-AH; Bullock-B
SO: **Neurotoxicology**, Vol. 5, No. 1, pages 59-66, 34 references, 1984
AB: The effect of **manganese** (7439965) inhalation on basal ganglia dopamine concentrations was studied in monkeys. Female rhesus-monkeys were exposed to 30 milligrams per cubic meter of **manganese-dioxide** (1313139) dust for 6 hours daily, 5 days a week, for 2 years. The animals were observed for clinical signs. After 2 years of exposure, the animals were killed and the brain was removed and dissected into the caudate, putamen, globus pallidus, and substantia nigra. Each brain part was assayed for dopamine and **manganese**. No abnormal behavior or **neurological** signs were noted in the monkeys during the exposure period. **Manganese-dioxide** caused a significant decrease in dopamine concentration in the caudate and globus pallidus. There was a slight, statistically insignificant decrease in dopamine concentration in the putamen. There was no difference in dopamine concentrations in the substantia nigra of the treated versus control animals. **Manganese-dioxide** caused a 60 to 80 percent increase in **manganese** concentration in all brain parts. The authors conclude that the dopamine system in the basal ganglia is susceptible to the effects of **manganese**. The amount of **manganese** inhaled and the length of exposure appear to determine whether abnormal **neurological** signs develop.
AN: 00141795

SF: NIOSH
TI: Differences In The **Neurotoxic** Effects Of **Manganese** During Development And Aging: Some Observations On Brain Regional **Neurotransmitter** And **Non-Neurotransmitter** Metabolism
AU: Lai-JCK; Leung-TKC; Lim-L
SO: **NeuroToxicology**, Vol. 5, No. 1, pages 37-47, 31 references, 1984
AB: The effects of chronic **manganese-chloride** (7773015) exposure on neurochemical parameters were studied in rats. Wistar-rats were administered **manganese-chloride-tetrahydrate** (13446349) at a concentration of 1 milligram per milliliter (mg/ml) in their drinking water for periods ranging up to one lifespan, about 2 years. The animals were killed at selected intervals, their brains were removed, dissected, and assayed for synaptosomal amine uptake, glutamic-acid-decarboxylase, choline-acetyltransferase, acetylcholinesterase (AChE), nicotinamide-adenine-dinucleotide (NAD) linked isocitric-dehydrogenase, and glucose-6-phosphate-dehydrogenase activities. **Manganese-chloride** caused transient, age dependent decrease in synaptosomal choline uptake in the hypothalamus and increases in uptake in the striatum. Synaptosomal noradrenaline and serotonin uptake were not affected. **Manganese-chloride** caused small decreases in choline-acetyltransferase activity in the cerebellum and midbrain after 2 months. The regional distribution of glutamic-acid-decarboxylase, AChE, or NAD linked isocitric-dehydrogenase in the brain was not affected. A 10mg/ml dose of **manganese-chloride** caused transient age dependent decreases in NAD linked isocitric-dehydrogenase activity, but had no effect on glucose-6-phosphate-dehydrogenase activities. In lifespan treatment with **manganese-chloride**, glutamic-acid-decarboxylase activity was decreased in the pons and medulla, choline-acetyltransferase activity was significantly increased in the cerebellum and cerebral cortex, and AChE activity was decreased in all brain parts. The authors conclude that encephalopathy induced by chronic **manganese** (7439965) poisoning affects brain development and aging in different ways. Lifespan treatment with **manganese-chloride** antagonizes age related decreases in NAD linked isocitric-dehydrogenase activities in most brain regions.
AN: 00142452

BF: NIOSH
TI: **Neurotransmitters** And **Neurotransmitter** Receptors In Developing And Adult Rats During **Manganese** Poisoning
AU: Seth-PK; Chandra-SV
SO: **NeuroToxicology**, Vol. 5, No. 1, pages 67-76, 24 references, 1984
AB: The effects of **manganese** (7439965) (**Mn**) on **neurotransmitters** and neuroreceptors in the adult and developing rodent are reviewed. Clinical, **neuropathological**, and biochemical evidence is presented to show that central **nervous** system dysfunction during **Mn** toxicity is due to disturbances in the **neurotransmitter** system. Effects of **Mn** on monoamine concentrations in the brain of experimental animals are summarized and alterations in the metabolism of the **neurotransmitter** relative to variations in species, dose, and mode of **Mn** exposure are noted. The high affinity binding of appropriate agonists and antagonists of the **neurotransmitter** is described. Data is presented to show the inability of the neonate to metabolize **Mn**, and the effect of **Mn** exposure on dopamine concentrations and receptor sensitivity are reviewed. Neonatal exposure to **Mn** produces a decrease in binding of spiroperidol to striatal membranes and of serotonin (50679) to frontal cortical membranes. Studies are described that suggest the involvement of dopaminergic, serotonergic, cholinergic, and gamma-aminobutyric-acid functions in **Mn neurotoxicity**. The dopaminergic system is more sensitive since the activity of this receptor is altered only at low doses of **Mn**. The mechanism by which the concentration of monoamines is altered after **Mn** exposure is discussed.
AN: 00142523

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SF: NIOSH
TI: Effect Of **Manganese** Treatment On The Levels Of **Neurotransmitters**, Hormones, And Neuropeptides: Modulation By Stress
AU: Hong-J-S; Hung-L-R; Seth-PK; Mason-G; Bondy-SC
SO: Environmental Research, Vol. 34, No. 2, pages 242-249, 40 reference, 1984
AB: The neurochemical and endocrine effects of repeated injections of **manganese** were studied in rats. Male Fischer-344-rats were intraperitoneally injected with saline or 15 milligrams per kilogram **manganese-chloride** (7773015) daily for 6 weeks. A control group was not injected or handled. Rats were weighed and sacrificed 24 hours after the last injection. Various brain regions were analyzed for **neurotransmitters** and their acid metabolites and neuropeptides, and serum was analyzed for hormones. Compared to non injected controls, body weight was reduced 10 percent in saline controls and 30 percent in treated animals. Prolactin was increased 2.2 times and luteinizing hormone was decreased 65 to 75 percent in both saline and **manganese** injected animals, while testosterone was decreased 70 percent in the **manganese** group only. Corticosterone more than doubled in the saline controls but was not affected in the **manganese** group. Neuropeptide concentrations in the striatum and frontal cortex were not affected by any treatment. In the hypothalamus, both treated and saline control groups showed increases of 40 percent in beta endorphin, 20 to 30 percent in substance-P, and 20 percent in met-enkephalin. Pituitary neurotensin was increased 60 percent in the **manganese** group. Striatal concentrations of dopamine, dihydroxyphenylacetic-acid, homovanillic-acid, serotonin, and 5-hydroxyindoleacetic-acid were 25 to 40 percent greater in the **manganese** group than in non injected controls; saline control values were intermediate to those of the other groups. The authors suggest that **manganese** predominantly attacks the hypothalamic/pituitary axis. The interaction of **neurotoxicant** exposure and stress may serve to unmask toxic effects that would otherwise be imperceptible.
AN: 00144316

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SF: CIS
TI: An epidemiological survey and clinical investigations on retired workers from **manganese** and ore grinders in Kyoto prefecture
AU: Sano-S; Yamashita-N; Kawanishi-S; Iguchi-H; Yoshinaga-T; Kojo-S; Tsukamoto-I; Fujita-H; Okamoto-H; Kato-N; et-al
SO: Journal of the Japanese Society for Hygiene June 1982, Vol.37, No.3, p.566-579. Illus. 32 ref.
AB: Most of the 162 retired workers had been employed in small factories under poor working conditions. 55% of them had been exposed for more than 11 years. 46% had been in retirement for 11-20 years and 27% for more than 21 years. 124 unexposed people living in the same region served as the control group. The incidence of subjective symptoms associated with chronic **manganese** poisoning such as emotional instability, psychomotor irritability and **neurologic** abnormalities was high in the exposure group, increasing with the period of exposure to **manganese** dust. 28% reported subjective symptoms while they were still employed, but 45% of them reported as much as 6 years after their retirement. Of the retired workers, 5 (3.1%) had parkinsonism, 3 (1.9%) showed symptoms of hemiparkinsonism, and 15 (9.3%) showed **neurological** symptoms including mask-like face, unbalanced gait, slurred speech and impairment of fine movement. 39% of the retired workers were diagnosed as having pneum
AN: 8301081

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86 of 118

SF: TOXBIB
TI: [Histopathological alteration of the central **nervous** system in rats, following long-term administration of **manganese** chloride--relation to the activity of the brain tyrosine hydroxylase]
AU: Nakashima-S
SO: No-To-Shinkei; VOL 35, ISS 1, 1983, P91-9
AB: Chronic **manganese** poisoning is characterized by mental and **extrapyramidal** disturbances. Parkinsonism-dementia complex (PD) on Guam is also manifested by progressive **extrapyramidal** syndrome and dementia. In PD, the reduced activities of catecholamine synthesizing enzymes in the brain has been demonstrated. On the other hand, the soil and water in Guam are rich in **manganese**, and one of the possible etiologic factors is trace element dysmetabolism in PD. The purpose of this paper is to clarify the effect of chronic **manganese** loading on the central **nervous** system. **Manganese** chloride (10 mg/ml of demineralized and distilled water) was administrated orally to Wistar female rats weighing 80-110 g. Six and 12 months after the administration, **manganese** loaded and control rats were sacrificed by perfusion for histological studies and by decapitation for the assay of tyrosine hydroxylase (TH) activity. The striatum, globus pallidus and substantia nigra were examined with electron microscopy. The brain for TH assay was dissected into four parts as the striatum, midbrain-thalamus, pons-medulla oblongata, and hypothalamus. Ultrastructural changes were overwhelmingly detected in the zona reticulata of the substantia nigra at 12 months. These changes were mainly composed of alterations of the postsynapse and neuronal soma--shrunken and electron dense dendrites accumulated degenerating materials and so-called simple atrophy-of-the-neuron. Alterations in the presynapse were extremely milder than those in the postsynapse and neuron. At both 6 and 12 months, no significant changes in the striatum and globus pallidus were detected except for irregular windings of the plasma membrane in the axon terminal of the globus pallidus at 12 months.(ABSTRACT TRUNCATED AT 250 WORDS)
AN: 84080174

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SF: TOXBIB
TI: Effect of low protein diet on **manganese neurotoxicity**: II. Brain GABA and seizure susceptibility.
AU: Ali-MM; Murthy-RC; Saxena-DK; Chandra-SV
SO: Neurobehav-Toxicol-Teratol; VOL 5, ISS 3, 1983, P385-9
AB: The effect of **manganese** (Mn2+, 3 mg/ml drinking water) on brain GABA content and electroshock seizure susceptibility in low (10% casein) and normal (21% casein) protein fed rats were investigated. **Manganese** exposure caused a decrease in the brain GABA content, lowered the seizure threshold and increased the seizure duration. These effects were more marked in the low protein fed rats. Diet rehabilitation caused a recovery in the GABA levels but has only a moderating effect on the seizure susceptibility and duration. An inverse correlation was observed between the brain GABA levels and seizure threshold. Results indicate a lowered GABA-ergic activity and a functional dysbalance between the GABA-ergic-dopaminergic neuronal systems in **manganese** toxicity.
AN: 83271722

SF: NIOSH
TI: **Manganese Neurotoxicity**: A Model For Free Radical Mediated Neurodegeneration
AU: Donaldson-J; McGregor-D; LaBella-F
SO: Canadian Journal of Physiology and Pharmacology, Vol. 60, No. 11, pages 1398-1405, 46 references, 1982
AB: Some effects of **manganese** (16397914) on the central **nervous** system were investigated in rats. Neonatal Sprague-Dawley-rats received daily injections of a control saline solution or 20 micrograms per gram body weight **manganese-chloride** (7773015) for 14 days. Rats were then killed and brains removed. The effects of **manganese** on central **nervous** system lipid peroxidation were observed through the malondialdehyde (542789) produced as an indicator of free radical activity. Individual regions of the brain were studied. Other male Sprague-Dawley-rats were injected intracerebroventricularly with saline or 25 micrograms **manganese-chloride**. At 1 hour animals were killed and the norepinephrine contents determined. There was considerable variation in the lipid peroxidation in various brain regions of newborn rats. High activity was found in the cerebellum and the hypothalamus, compared with the medulla oblongata and the midbrain. Treatment with **manganese** resulted in a drastic fall in lipid peroxidation which ranged from about 40 percent in the olfactory bulb to almost 100 percent in the striatum. The contents of norepinephrine fell significantly in the hypothalamus of **manganese** treated rats. The authors conclude that **manganese** reduces lipid peroxidation and the synthesis of norepinephrine in the rat brain.
AN: 00161236

SF: NIOSH
TI: **Neurotoxic** Effects Of **Manganese**: Studies On Cell Cultures, Tissue Homogenates And Intact Animals
AU: Heilbronn-E; Eriksson-H; Haggblad-J
SO: Neurobehavioral Toxicology and Teratology, Vol. 4, No. 6, pages 655-658, 27 references, 1982
AB: Studies on the effects of **manganese** (7439965) on neonatal and adult rats during chronic and acute exposure are reviewed. In early animal experiments, 3 day old rats intubated with 75 to 150 milligrams (mg) labeled **manganese** over several weeks were slow in gaining weight compared with controls. Brains of newborn animals took up considerably more **manganese** than did those of older animals. A study on the localization of **manganese** is discussed. Uptake from the gastrointestinal tract is slow, but the brain accumulates **manganese** in certain areas faster than in others. A study of rats after 30 days of exposure to **manganese** found the brain accumulation to be highest in the striatum, followed by the midbrain, thalamus, olfactory bulb, and cerebellum. The high percentage increase found in the corpus callosum suggests an affinity of **manganese** for myelinated fibers. Preliminary behavioral test results correlated to transmitter studies on live animals indicate increased motor activity in rats after several weeks of daily exposure to 150mg **manganese-chloride** (7773015). Increased contents of gamma-aminobutyric-acid (56122) in the striatum of rats exposed to **manganese** for 2 months have been observed. **Manganese** has the ability to be involved in several reduction/oxidation reactions. **Manganese** was found to inhibit lipid peroxidation when performed on adrenergic and cholinergic neuroblastoma cells in culture. In human studies, severe symptoms include those for **manganese** madness and those similar to Parkinsonism. Late peripheral **nerve** lesions from **manganese** have also been described. Other studies suggest that **manganese** displaces certain other ions present in the brain. The authors conclude that the central catecholaminergic system is attacked by **manganese** compounds.
AN: 00145058

SR: Nitem
TI: Alterations In Brain Dopamine And GABA Following Inorganic Or Organic **Manganese** Administration
AU: Pianutsos-G; Murray-MT
SO: **Neurotoxicology**, Vol. 3, No. 3, pages 75-82, 24 references, 1982

AB: The effects of **manganese-chloride** (7773015) (MnCl2) and **methylcyclopentadienyl-manganese-tricabonyl** (12108133) (MMT) on brain dopamine (DA) and gamma-aminobutyric-acid (GABA) were investigated in male CD-1 mice. Mice received 4 percent MnCl2 in diets for 6 months or MMT subcutaneously at 10, 20, and 80 milligrams per kilogram (mg/kg) on alternate days for 3 weeks. Controls received subcutaneous injections of propylene-glycol. After treatment mice were killed and brain GABA was assayed. DA and choline-acetyltransferase (CAT) were measured. MnCl2 administered in the feed reduced brain DA concentrations significantly. The DA of striatum nigra and olfactory tubercles were reduced by 21.5 and 18 percent, respectively, compared with controls. No changes were seen after 1 or 2 months. MMT injected at 20 and 80mg/kg reduced striatal DA by 10 and 23 percent, respectively. The olfactory tubercle was more resistant to the DA depleting effects of MMT. MnCl2 elevated concentrations of GABA in striatum and su
bstantia nigra, while MMT produced a similar effect but only at 80mg/kg dose. The cerebellum concentration of GABA was not affected by either compound. Acute injection of MMT failed to alter GABA concentrations in the brain. CAT remained unchanged in all regions of the brain after MnCl2 treatment, suggesting that cholinergic neurons were spared the **neurotoxic** effects of **manganese**. The authors conclude that long term treatments with MnCl2 and MMT induce changes in **neurotransmitter** concentrations.
AN: 00140115

Output generated from Compact Cambridge: POLTOX 1987 - March 1990
Search Strategy:
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DOCUMENT 41 of 95:

AU: AUTHOR
Eriksson H; Magiste K; Plantin L-O; Fonnum F; Hedstrom K-G;
Theodorsson-Norheim E; Kristensson K; Stalberg E; Heilbronn E
TI: TITLE
Effects of Manganese Oxide on Monkeys as Revealed by a Combined Neurochemical, Histological and Neurophysiological Evaluation
SO: SOURCE
Archives of Toxicology, Vol. 61, No. 1, pages 46-52, 41 references, 1987
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
The neurochemical, neurophysiological, and histological effects of high doses of manganese-oxide (1317357) were studied in monkeys. Manganese-oxide was administered by subcutaneous injection in a suspension of olive-oil. The animals received a total of 8 grams of manganese (7439965) over 5 months. Evaluation parameters included animal behavior as recorded on videotape, manganese levels in various brain areas, monoamine analysis, enzymatic activities of DOPA-decarboxylase (DDC), choline-acetyltransferase (CAT), and glutamic-acid-decarboxylase (GAD), glutathione analysis, and needle electromyographic analysis of the tibial anterior and quadriceps femoris muscles after stimulation of the peroneal nerve. Behavioral changes included established hyperactivity after 2 months and hypoactivity after 5 months. Motor weakness, tremor, and myoclonus were observed during the later stages. Exposed monkeys showed significant losses of neurons and concomitant astrogliosis in the pallidum. Blood manganese levels were approximately 20 times the control values throughout the experiment, and different brain regions showed different susceptibilities to manganese uptake. The highest levels of brain manganese were reported in the globus pallidus, caudate nucleus, substantia nigra, cerebral cortex, and cerebellum, and significant reductions of dopaminergic and serotoninergic chemicals were observed in these areas. The activities of DDC and CAT were reduced in the putamen and globus pallidus, and the activity of GAD appeared unaffected by the treatment. Brain glutathione levels were depressed in the manganese exposed animals. There was no evidence of peripheral neuropathy or disturbed neuromuscular transmission. ABSTRACT.

Output generated from Compact Cambridge: POLTOX 1987 - March 1990.
Search Strategy:
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DOCUMENT 40 of 85:

AU: AUTHOR
Cox DN; Traiger GJ; Jacober BP; Hanzlik RP
TI: TITLE
Comparison of the Toxicity of Methylcyclopentadienyl Manganese Tricarbonyl with that of Its Two Major Metabolites
SO: SOURCE
Toxicology Letters, Vol. 39, No. 1, pages 1-5, 9 references, 1987
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
Pneumotoxicity and lethality resulting from administration of methylcyclopentadienyl-manganese-tricarbonyl (12108133) (MMT) and its two major metabolites, hydroxymethylcyclopentadienyl-manganese-tricarbonyl (CMT-CH2OH) and carboxycyclopetadienyl-manganese-tricarbonyl (12082074) (CMT-COOH), were compared in Sprague-Dawley-rats. Each dose of each compound was administered to a group of four rats which were then observed for 14 days. MMT was administered by intraperitoneal (ip) injection of single doses of between 6.0 and 37.4mg/kg. At all doses except the lowest, significant tonic clonic convulsive activity was observed, and mortality usually occurred within 15 minutes of dosing. The 50 percent lethal dose of MMT was calculated to be 12.1mg/kg. Extensive mottling, hemorrhage and distention of the lungs were observed on gross pathological evaluation. Neither CMT-CH2OH, administered ip at doses of between 100 and 400mg/kg, nor CMT-COOH, administered ip at a dose of 250mg/kg, resulted in significant toxicity except at the highest dose of CMT-CH2OH. In this case, two of the animals experienced convulsions and died. The authors conclude that MMT is much more toxic than either of its two metabolites. They suggest that the differences in toxicity may be due to changes in solubility of the metabolites allowing for decreased distribution into the central nervous system and a more rapid excretion rate. They conclude that the oxidative metabolism of MMT is an important detoxifying pathway. ABSTRACT.

SF: TOXBIB
TI: Fertility of male workers exposed to mercury vapor or to **manganese** dust: a questionnaire study.
AU: Lauwerys-R; Roels-H; Genet-P; Toussaint-G; Bouckaert-A; De-Cooman-S
SO: Am-J-Ind-Med; VOL 7, ISS 2, 1985, P171-6
AB: The fertility of male workers exposed to mercury vapor or to **manganese** dust was assessed with the use of the questionnaire developed by Levine et al (1966). In the mercury group (concentration of mercury in urine ranging from 5.1 to 272.1 micrograms/g creatinine), no statistically significant difference was found between the observed number of children and that expected on the basis of the reproductive experience of a well-matched control group. On the contrary, by comparison with their corresponding controls, the **manganese-exposed** workers exhibited a statistically significant deficit in the number of children during their period of exposure to the metal. The airborne concentration of **manganese** dusts at the different workplaces ranged from 0.07 to 8.61 mg/m3 with a geometric mean of 0.94 mg/m3.
AN: 85145863

SF: NIOSH
TI: Chronic **Manganese** Poisoning: A **Neuropathological** Study with Determination of **Manganese** Distribution in the Brain
AU: Yamada-M; Ohno-S; Okayasu-I; Okeda-R; Hatakeyama-S; Watanabe-H; Ushio-K; Tsukagoshi-H
SO: Acta **Neuropathologica**, Vol. 70, No. 3-4, page 273-278, 27 references, 1986
AB: An autopsy case of chronic **manganese** (7439965) poisoning (CMP) was examined and the topographical distribution of **manganese** in the brain was determined. The patient had a history of occupational exposure to **manganese** for 12 years. **Manganese** was increased in the serum and urine. The major **neuropathological** change was degeneration of the basal ganglia, in which the pallidum, especially in its medial segment, was severely damaged. The substantia nigra was intact. There was no overall increase in **manganese** concentration in the brain. The **manganese** distribution did not show any significantly high value in the basal ganglia and cerebral white matter. **Manganese** concentration was increased in the gray matter of the cerebral cortex and decreased in the basal ganglia. The authors conclude that the continuance of **neurological** disorders in CMP is not linked to elevation of **manganese** concentration itself in the brain. They also suggest that chelation therapy might possibly be effective only in the early phase of CMP, during which the brain damage would be reversible.
AN: 00163957

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AF: NIOSH
TI: The Effects Of **Manganese** On The Cholinergic Receptor In Vivo And In Vitro May Be Mediated Through Modulation Of Free Radicals
AU: Donaldson-J; LaBella-FS
SO: **NeuroToxicology**, Vol. 5, No. 1, pages 105-112, 30 references, 1984
AB: The effects of **manganese** (7439965) on the central **nervous** receptor were studied in-vitro and in-vivo in rats. Whole rat brain homogenates were incubated in a medium containing dopamine, **manganese-chloride** (7773015), and tritium (H-3) labelled 3-quinuclidinyl-benzilate (QNB). Following incubation, the mixture was assayed for QNB binding to the brain cells by determining H-3 activity. Neonatal rats of unspecified strain were injected subcutaneously with 20 micrograms per gram **manganese-chloride** daily for 14 days. The rats were then killed and their brains were removed, dissected into various parts, and assayed for QNB binding. Brain homogenates were prepared and assayed for lipid peroxidation. In-vitro QNB binding in rat brain homogenates was reduced by **manganese-chloride**. **Manganese** caused a significant increase in QNB binding in striatal tissue of neonatal rats. No effect was seen in other brain regions. Lipid peroxidation was significantly reduced in all brain regions of neonatal rats. The authors conclude that **manganese** can act either as an oxidant or a powerful antioxidant in rat brains. Which role **manganese** takes may depend on the redox status of a particular brain region as well as on the amount of **manganese** deposited there.
AN: 00142077

BF: ETIC
TI: EFFECT OF **MANGANESE** CHLORIDE INTOXICATION ON GAMMA-AMINOBUTYRIC ACID LEVEL AND SYNTHESIS IN THE RAT BRAIN DURING PREGNANCY AND LACTATION
AU: KOSICKA-B; KITTEL-M; SMIALEK-M
SO: NEUROPATOL POL; 23:201-209,1985
AB: ETIC/ORNL
AN: 85040290

34 of 118

BF: NIOSH
TI: Brain **Manganese** Accumulation Following Systemic Administration Of Different Forms
AU: Gianutsos-G; Seltzer-MD; Saymeh-R; Wang-Wu-M-L; Michel-RG
SO: Archives of Toxicology, Vol. 57, No. 4, pages 272-275, 11 reference, 1985
AB: Blood and brain accumulation of **manganese** (7439965) was studied in mice. Male CD-1-mice were injected subcutaneously (sc) with **manganese-dichloride** (7773015), **manganese-oxide** (11129605), or **methylcyclopentadienyl-manganese-tricarbonyl** (12108133) in doses corresponding to 0.2 or 0.4 milliequivalent of **manganese** per kilogram (meq/kg). The mice were killed 2 hours to 21 days after injection. Blood and brain managanese concentrations were measured. Mice were given one to three weekly sc injections of 0.4meq/kg managanese as **manganese-oxide** or **manganese-chloride**. Blood and brain **manganese** concentrations were determined as before. Brain **manganese** concentrations were elevated to at least twice the control value 4 to 8 hours after administration, regardless of the chemical form of **manganese** injected. Blood **manganese** concentrations reached their maximum value 4 hours after injection of the oxide and remained elevated for 1 week. Blood **manganese** concentrations after **manganese-chloride** injection peaked at more than 10,000 percent of the control value within 1 hour and gradually declined over the course of 1 week; however, they were still 740 percent of the control value after 1 week. Peak brain concentrations occurred 24 hours after injection and remained elevated for at least 1 week. Repeated injections caused further increases in both brain and blood **manganese** concentrations. Elevated brain **manganese** concentrations after repeated injections decreased more slowly than after a single injection. Brain **manganese** concentrations after 21 days were comparable to those observed 1 week after a single injection. The authors suggest that the slowly developing **neurotoxicity** in response to **manganese** exposure may be due to prolonged retention of **manganese** by the brain.
AN: 00154536

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Search Strategy:
MANGANESE[ALL] OR MN[ALL] AND ((NEUROTOX*[ALL] OR NEUROTRANSMIT*[ALL] OR NEUROLOG*[ALL] OR NEUROPATH*[ALL]) OR NERVE[ALL] OR NERVES[ALL] OR NERVOUS[ALL]) AND MANGANESE[ALL]
DOCUMENT 61 of 85:

AU: AUTHOR
Fishman BE; McGinley PA; Gianutsos G
TI: TITLE
Neurotoxic effects of methylcyclopentadienyl manganese tricarbonyl (MMT) in the mouse: basis of MMT-induced seizure activity.
SO: SOURCE
Toxicology; VOL 45, ISS 2, 1987, P193-201
PY: PUBLICATION YEAR
1987
LA: LANGUAGE
English
AB: ABSTRACT
Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese-containing compound which is used as an additive in unleaded gasoline. One neurotoxic effect of MMT in mice is seizure activity. In this study, seizures were observed in mice treated with MMT in propylene glycol or corn oil. The LD50 associated with seizure activity was lower in mice receiving MMT in propylene glycol (152 mg/kg) than in those receiving MMT in corn oil (999 mg/kg). Manganese concentrations in the brains of mice which showed seizure activity due to MMT were higher than in those that did not (2.45 micrograms/g vs. 1.14 micrograms/g for MMT treated in propylene glycol and 3.25 micrograms/g vs. 1.63 micrograms/g for MMT in corn oil). Mice treated with manganese chloride (MnCl2) showed increases in brain manganese comparable to those of the mice showing seizure activity due to MMT, but exhibited no sign of seizure activity. MMT in non-lethal seizure-inducing doses had no effect on the accumulation of 4-aminobutyric acid (GABA) in mouse brain. However, MMT inhibited the binding of t-[3H]t-butylbicycloorthobenzoate [3H]-TBOB (a ligand for the GABA-A-receptor linked chloride channel) in mouse brain membranes with an IC50 value of 22.8 microM. The data suggest that MMT (organic manganese) or a closely related metabolite and not elemental manganese itself is responsible for the seizure activity observed. The seizure activity may be the result of an inhibitory effect of MMT at the GABA-A receptor linked chloride channel. ABSTRACT.

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DOCUMENT 29 of 85:

AU: AUTHOR
Ferraz HB; Bertolucci PH; Pereira JS; Lima JG; Andrade LA
TI: TITLE
Chronic exposure to the fungicide maneb may produce symptoms and signs of CNS manganese intoxication.
SO: SOURCE
Neurology; VOL 38, ISS 4, 1988, P550-3
PY: PUBLICATION YEAR
1988
LA: LANGUAGE
English
AB: ABSTRACT
Manganese (Mn) poisoning, a well-known hazard in miners and industrial workers, shares many features with Parkinson's disease. Two young agricultural workers with a parkinsonian syndrome, who mentioned exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate), led us to investigate a new possible source of Mn intoxication. Fifty male rural workers with occupational exposure to maneb were compared with 19 rural workers without fungicide-exposure. We noted significantly higher prevalence of plastic rigidity with cogwheel phenomenon, headache, fatigue, nervousness, memory complaints, and sleepiness in the exposed group. In addition, we saw other neurologic signs, such as postural tremor, cerebellar signs, and bradykinesia, although without statistical significance. The data suggest that occupational exposure to pesticides containing Mn is a possible source of Mn intoxication of the CNS. ABSTRACT.

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DOCUMENT 32 of 85:

AU: AUTHOR
Liccione JJ; Maines MD
TI: TITLE
Selective Vulnerability of Glutathione Metabolism and Cellular Defense Mechanisms in Rat Striatum to Manganese
SO: SOURCE
Journal of Pharmacology and Experimental Therapeutics, Vol. 247, No. 1, pages 156-161, 39 references, 1988
PY: PUBLICATION YEAR
1988
LA: LANGUAGE
English
AB: ABSTRACT
The effects of manganese (7439965) on whole brain and striatal glutathione (GSH) metabolism and cellular defense mechanisms were studied in rats. Adult male Sprague-Dawley-rats were administered 1750 micromoles per kilogram manganous-chloride (7773015) over a 7 day period by subcutaneously implanted osmotic minipumps. They were killed at the end of the dosing period, the brains were removed, and the striatum was dissected out. Whole brain and striatal homogenates and the mitochondrial, microsomal, and cytosolic fractions were prepared and assayed for catalase, glutathione-peroxidase (GSHPx), oxidized-glutathione-reductase (GSSG-red), gamma-glutamyl-transpeptidase (GGT), gamma-glutamylcysteine-synthetase (GGTcyase), GSH, dopamine, 3,4-dihydroxyphenylacetic-acid (DHPAA), 4-hydroxy-3-methylphenylacetic-acid (OHMePAA), and manganese. Manganous-chloride significantly reduced the concentrations of dopamine, DHPAA, and OHMePAA in the striatum. The manganese contents of the mitochondrial fraction of the whole brain and striatum were significantly increased. Manganese significantly reduced whole brain and striatal cytosolic and mitochondrial GSHPx activity, the greatest reduction occurring in the striatal mitochondria. Catalase activity was decreased only in the striatum. Striatal GSH content was reduced sharply; however, whole brain GSH was reduced only slightly. Manganese increased whole brain and striatal GGT activity and decreased whole brain and striatal GSSG-red activity. The increases in GGT activity were similar in both the whole brain and striatum, whereas the decrease in GSSG-red was greater in the striatum. GGTcyase activity was not significantly affected by manganese. The authors conclude that the cellular defense mechanisms of certain enzymes important in GSH metabolism are significantly altered by manganese in the brain of rats, especially in the striatum. These changes may be involved in manganese neurotoxicity. ABSTRACT.

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DOCUMENT 20 of 65:

AU: AUTHOR
Parenti M; Rusconi L; Cappabianca V; Parati EA; Groppetti A
TI: TITLE
Role of dopamine in manganese neurotoxicity.
SO: SOURCE
Brain Res; VOL 473, ISS 2, 1988, P236-40
PY: PUBLICATION YEAR
1988
LA: LANGUAGE
English
AB: ABSTRACT
Manganese chloride increased cell mortality when added to human fibroblast cultures. The toxicity of the metal was greatly enhanced by dopamine; this effect was antagonized by the presence in the culture medium of catalase and superoxide dismutase enzymes. Manganese chloride also caused a marked decrease of striatal dopamine concentrations when infused into rat substantia nigra. Manganese neurotoxicity was lowered by pretreating the animals with drugs that reduced striatal dopamine turnover rate. Administration of an antioxidant, such as vitamin E, also partially prevented striatal dopamine decline induced by intranigral manganese infusion. Therefore, the decreased availability or autoxidation of dopamine attenuated manganese neurotoxicity. These findings are in agreement with previous observations suggesting that manganese increases toxic products originating from dopamine catabolism. ABSTRACT.

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DOCUMENT 17 of 85:

AU: AUTHOR
Haug BA; Schoenle PW; Karch BJ; Bardosi A; Holzgraefe M
TI: TITLE
Morvan's fibrillary chorea. A case with possible manganese poisoning.
SO: SOURCE
Clin Neurol Neurosurg; VOL 91, ISS 1, 1989, P53-9
PY: PUBLICATION YEAR
1989
LA: LANGUAGE
English
AB: ABSTRACT
The clinical picture of Morvan's fibrillary chorea includes a. spontaneous muscular activity resulting from repetitive motor unit action potentials of peripheral origin (multiplets), b. autonomic dysregulation with profuse hyperhidrosis, and c. central nervous system involvement as shown by severe insomnia and hallucinosis. A case featuring all these symptoms is presented. Whereas known causative factors range from gold or mercury poisoning to autoimmune disorders, the presented case is the first one in which chronic manganese intoxication (occupational exposure) seems to be implicated. Manganese has been found to inhibit acetylcholine esterase, and, as a consequence, may produce peripheral and central cholinergic hyperactivity.
ABSTRACT.

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DOCUMENT 1 of 154:

AU: AUTHOR
Newland MC; Ceckler TL; Kordower JH; Weiss B
TI: TITLE
Visualizing manganese in the primate basal ganglia with magnetic resonance imaging.
SO: SOURCE
Exp Neurol; VOL 106, ISS 3, 1989, P251-8
PY: PUBLICATION YEAR
1989
LA: LANGUAGE
English
AB: ABSTRACT
The paramagnetism of manganese was exploited to obtain proton nuclear magnetic resonance (MR) images of manganese-rich tissue in the central nervous system in vivo. One Macaca fascicularis monkey inhaled MnCl2 aerosol prior to imaging. A second M. fascicularis and two Cebus apellas were administered MnCl2 in various doses intravenously. The monkeys' brains were imaged before and after manganese administration in coronal and horizontal planes that included the basal ganglia and substantia nigra. A T1-weighted pulse sequence exploited manganese's reduction of spin-lattice relaxation times and clearly distinguished several separate and specific regions after manganese administration: the caudate nucleus, the lenticular nuclei, the substantia nigra, a region corresponding to subthalamic nucleus and ventromedial hypothalamus, and the pituitary gland. The kinetics of manganese accumulation were important in determining the imaged intensity of these regions but the route of parenteral administration was not. Spin-lattice relaxation times showed that T1 was shortened at lower doses of manganese and remained shortened longer in the globus pallidus and pituitary gland while little effect appeared in gray and white matter. T1 effects in caudate and putamen effects were intermediate. These data suggest selective affinity for manganese in globus pallidus and pituitary. ABSTRACT.